The specification has been amended to add sequence identification numbers. These amendments are merely formalities. In addition, the specification has been amended to correct an obvious typographical error at page 17, lines 29-30. Support for the amendment can be found throughout the specification, for example, at page 17, line 31, through page 18, line 2, and at page 18, lines 6-14. The amendments to the specification do not add new matter. Accordingly, Applicants respectfully request that the Examiner enter the amendments.

Applicants are concurrently submitting a copy of the Sequence Listing, in paper and computer readable versions, and a statement to satisfy the requirements of 37 CFR § 1.821.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 13 and 28 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting the phrase "low resolution." Applicants respectfully traverse the rejection for the reasons set forth below.

Applicants submit that the phrase "low resolution" is clear to those skilled in the art in light of the teaching of the specification. For example, criteria regarding the phrase "low resolution" can be found at page 17, lines 27-31, which teaches that "the term "low resolution" when referring to a mass spectrum is intended to mean that the mass determination is accurate at about twenty-five parts per million (ppm) or greater of component ion fragments. In addition, for example, the specification

teaches at page 18, lines 6-14, that "the following range of mass accuracy at 100 Da can be considered low mass accuracy: about 25 parts per million (ppm) or greater than 25 ppm." Therefore, the specification discloses specific criteria regarding the term "low resolution." Accordingly, Applicants respectfully request that the above ground of rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-4, 6, 8-13, 15-19, 21, and 23-29 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Gygi et al. The Office Action alleges that Gygi et al. describes an approach for the accurate quantification and concurrent identification of the individual proteins within a complex mixture utilizing isotope-coded affinity tags (ICATs) and tandem mass spectrometry. Applicants respectfully traverse this ground of rejection.

The claimed invention is directed to methods for determining the amino acid sequence of a polypeptide. Each of the claims under examination include adding to a graph a labeled weighted directed edge that combines properties of paired signals. The specification teaches, for example, at page 13, lines 10-13, that a paired signal can consist of two mass spectra signals derived from the same polypeptide fragment that has been differentially labeled.

In contrast, Gygi et al. determine amino acid sequence using a single series of spectra, not data from paired signals. For example, on page 995, the last panel of Figure 2 shows a single series of spectra which is used to determine sequence information. Gygi et al. go on to teach that the resulting spectra are "automatically correlated with sequence databases to identify the protein from which the sequenced peptide originated" (see page 995, column 1). In contrast, the claimed methods do not require database searching to obtain an amino acid sequence by mass spectrometry because the claimed methods utilize paired signals to generate such sequence information.

The only context in which the Gygi et al. publication utilizes paired signals is to determine the relative quantities of particular peptides in the two samples that were originally labeled. Determining the relative quantities of peptide species is distinct from amino acid sequence determination because determination of the quantity of a peptide does not give any information as to the order of amino acids in the peptide. Thus, the publication by Gygi et al. does not teach paired signals for determining amino acid sequence. Since the publication by Gygi et al. does not teach each element of the claimed invention, the Gygi et al. reference can not anticipate the claimed invention. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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APPENDIX A

MARKED UP VERSION OF THE SPECIFICATION

A marked up version of the specification follows. Text to be added is underlined and text to be deleted is in brackets.

Please replace the paragraph starting on page 5, line 7, and ending on page 5, line 8, with the following paragraph:

Figure 3 shows a schematic of de novo sequence algorithm process for GNLQIDFADPSR **(SEQ ID NO: 11)**.

Please replace the paragraph starting on page 55, line 9, and ending on page 55, line 23, with the following paragraph:

An additional optional feature in the method is the inclusion of internal multiple amino acid edges to account for degenerate sequence. These edges can enable a direct jump over a missing ion edge and assign that edge a degenerate amino acid designation. For example, a *de novo* derived sequence, -PDNAVITIG- **(SEQ ID NO: 8)**, from a carboxyl-terminus labeled peptide can differ from the true sequence, SYELPDGQVITIGNER **(SEQ ID NO: 7)**, at a di-amino acid stretch (i.e. NA vs. GQ) due to preferential cleavage at the leucinyl-proline bond that results in a missing y-9 fragment ion. A method with internal multiple

amino acid edges can jump from the y-8 to the y-10 ion and the resulting sequence will have a degenerate amino acid at the y-9 position so that the resulting sequence will include the correct sequence.

Please replace the paragraph starting on page 66, line 6, and ending on page 66, line 17, with the following paragraph:

Table 1: Relative Abundance and Sequence of Select $[M + 2H]^{2+}$ ions

d0-/d3-ester	Parent Protein	Database Sequence	NO:	*de novo* sequence	NO:
1.0:1.0	VIME_HUMAN	QDVDNASLAR	1	QDVDNAS-	2
		QQYESVAAK	3	QQYESVAAK	3
1.0:1.1	ACTA_HUMAN	QEYDESGPSIVHR	4	QEYDESGP-	5
		AGFAGDDAPR	6	AGFAGDDAPR	6
		SYELPDGQVITIGNER	7	-PDNAVITIG-	8
1.0:1.2	GB01_HUMAN	LLLLGAGESGK	9	LLLLGAGE-	10
		GNLQIDFADPSR	11	-IDFAD-	12
1.0:1.7*	MYSN_HUMAN	DLEAHIDSANK	13	DLEAHID-	14

*Not an average.

NO: indicates sequence identification number (SEQ ID NO:)

Please replace the paragraph starting on page 17, line 27, and ending on page 18, line 2, with the following paragraph:

As used herein, the term "low resolution" when referring to a mass spectrum is intended to mean that the mass determination is accurate at about twenty-five **[one]** part**s** per million (ppm) or greater of component ion fragments. A mass spectrometer that provides an accuracy of less than about 25 ppm is considered to provide high resolution spectra.